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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

02075998.1

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 02075998.1
Demande no:

Anmeldetag:
Date of filing: 11.03.02
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Small molecule entry inhibitors

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D213/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE TR

SMALL MOLECULE ENTRY INHIBITORS

The present invention generally relates to small molecules as inhibitors of a virus, such as HIV, and host cell membranes. It further relates to pharmaceutical compositions containing them, as well as their use as medicines. The present invention also relates to their chemical preparation

The number of people living with HIV/AIDS totaled in December 2001 about 40 million of which more than 37 million adults and about 2.7 million children under 15 years old. The people newly infected with HIV in 2001 alone rose to 5 million whereas there were in 2001 3 million AIDS deaths. Current chemotherapy for these people infected with HIV/AIDS employs the inhibitors of the viral reverse transcriptase (RT) and protease enzymes. In view of the emergence of HIV strains resistant to the current generation of RT and protease inhibitors, there exists an increasing need for the development of new antivirals with novel mechanisms of action.

One of the new areas of emerging antiretrovirals is the area of the "entry inhibitors". These drugs are designed to block HIV from entering the human cell by interfering with various phases of attachment and fusion between HIV and the cell. The entry process can be divided in three sequentially distinct steps (1) binding of the virus envelope protein gp120 to the CD4 receptor on the host cell, (2) binding of the virus envelope protein gp120 to the co-receptors (CXCR4 / CCR5) on the host cell, and (3) fusion of the virus and the host cell membranes, mediated by the virus envelope protein gp41.

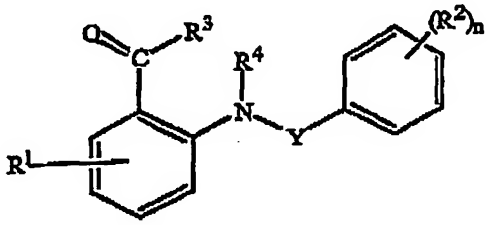
Several (co)receptor inhibitors and two fusion inhibitors, T20 and T1249 (Trimeris, Durham, NC, USA), peptides based on elements of gp41, are currently in the final stages of clinical development. The successful proof-of-principle studies conducted with T20 made that HIV fusion has been validated as a clinically relevant target.

However, the use of peptides has many drawbacks when they are to be developed as pharmaceutically acceptable drugs. Therefore, there is a need to develop small molecules which may block HIV from entering the human cell by interfering with various phases of attachment and fusion between HIV and the cell.

WO 00/04903, published February 3, 2000, concerns a method of inhibiting HIV-1 infection comprising the administering to a patient specific tetrazol derivates having a

molecular weight of between 200 and 650 daltons and which inhibit the binding of gp120 to CD4.

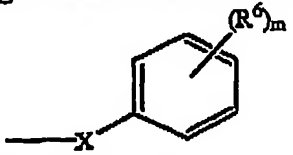
Unexpectedly, it was found that the compounds of the present invention are inhibitors of the entry process of the HIV virus into the host cell. Said compounds having the formula



(I)

their N-oxide forms, stereochemical isomers, salts and prodrugs thereof,
wherein

R^1 represents halogen, hydrogen or a radical of formula (II)



(II)

R^2 represents alkyl, alkenyl, alkynyl, hydroxy, halogen, nitro, cyano, amino, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, R^8-O-, R^8-S-, R^8-S(=O)2-, R^8-C(=O)-, R^8-C(=S)-, R^8-C(=NH)-, R^8-C(=NCN)-, R^8-NH-, $(R^8)_2$-N-, HO-C(=O)-, NH_2-C(=O)-, NH_2-S(=O)$_2$-, NH_2-C(=S)-, NH_2-C(=NH)-, NH_2-C(=NCN)-, R^8-NR^4-C(=O)-, R^8-NR^4-S(=O)$_2$-, R^8-O-C(=O)-, R^8-C(=O)-NR^4-, R^8-S(=O)$_2$-NR^4- or R^8-C(=O)-O-;

R^5 represents alkyl, alkenyl, alkynyl, hydroxy, halogen, nitro, cyano, amino, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, R^8-O-, R^8-S-, R^8-S(=O)2-, R^8-C(=O)-, R^8-C(=S)-, R^8-C(=NH)-, R^8-C(=NCN)-, R^8-NH-, $(R^8)_2$-N-, HO-C(=O)-, NH_2-C(=O)-, NH_2-S(=O)$_2$-, NH_2-C(=S)-, NH_2-C(=NH)-, NH_2-C(=NCN)-, R^8-NR^4-C(=O)-, R^8-NR^4-S(=O)$_2$-, R^8-O-C(=O)-, R^8-C(=O)-NR^4-, R^8-S(=O)$_2$-NR^4- or R^8-C(=O)-O-;

R^4 represents hydrogen, alkyl or cycloalkyl;

R^3 represents hydroxy, amino, alkyloxy, cycloalkyloxy or mono- or disubstituted amino whereby the substituents can be selected from alkyl and cycloalkyl;
R^7 represents hydroxy, amino, alkyloxy, cycloalkyloxy or mono- or disubstituted amino whereby the substituents can be selected from alkyl and cycloalkyl;

R^8 represents alkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl;

R^6 is hydrogen, amino, R^7-C(=O)-, R^8-S(=O)$_2$-NH-, R^8-C(=O)-NH-, R^8-C(=S)-NH-, R^8-C(=NH)-NH-, R^8-C(=NCN)-NH-, R^8-O-C(=O)-NH-, R^8-O-alkanediyl-C(=O)-NH-, R^8-alkanediyl-S(=O)$_2$-NH-, aryl-alkanediyl-C(=O)-NH-, heteroaryl-alkanediyl-C(=O)-NH-, cycloalkyl-alkanediyl-C(=O)-NH-, heterocycloalkyl-alkanediyl-C(=O)-NH-, or alkyl substituted with amino, R^7-C(=O)-, R^8-S(=O)$_2$-NH-, R^8-C(=O)-NH-, R^8-C(=S)-NH-, R^8-C(=NH)-NH-, R^8-C(=NCN)-NH-, R^8-O-C(=O)-NH-, R^8-O-alkanediyl-C(=O)-NH-, R^8-alkanediyl-S(=O)$_2$-NH-, aryl-C_{1-6}alkanediyl-C(=O)-NH-, heteroaryl-alkanediyl-C(=O)-NH-, cycloalkyl-alkanediyl-C(=O)-NH- or heterocycloalkyl-alkanediyl-C(=O)-NH-;

Y represents alkanediyl, -C(=O)-, -C(=S)-, -C(=NH)-, -C(=NCN)-, -S(=O)-, -S(=O)$_2$-, -C(=O)-CH$_2$-O-, -C(=O)-O-, -C(=O)-(CH$_2$)$_p$-;

X is a direct bond, -O- , -S-, -S(=O)$_2$-, -O-S(=O)$_2$, -S(=O)$_2$-O-, -NH-S(=O)$_2$, -S(=O)$_2$-NH-, -C(=O)-, -C(=S)-, -C(=NH)-, -C(=NCN)-, -O-C(=O), -C(=O)-O-, -NH-C(=O), -C(=O)-NH- or alkanediyl;

n is zero, 1 or 2;

p is an integer from 1 to 4;

Whenever the term "substituted" is used in defining the entry inhibitor of formula (I), it is meant to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group, provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a chemically stable compound, i.e. a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a therapeutic agent.

As used herein, the term "halo" or "halogen" as a group or part of a group is generic for fluoro, chloro, bromo or iodo.

The term "alkyl", alone or in combination, means straight and branched chained saturated hydrocarbon radicals containing from 1 to 10 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably 1 to 6 carbon atoms, and even more preferably 1 to 4 carbon atoms. Examples of such alkyl radicals include methyl, ethyl, n-propyl, isopropyl n-butyl, isobutyl, set-butyl, tert-butyl, 2-methylbutyl, pentyl, iso-amyl, hexyl, 3-methylpentyl, octyl and the like.

The term "alkanediyl", alone or in combination, defines bivalent straight and branched chained saturated hydrocarbon radicals containing from 1 to 10 carbon atoms, preferably from 1 to 8 carbon atoms, more preferably 1 to 6 carbon atoms and even more preferably 1 to 4 carbon atoms, such as, for example, methylene, ethan-1,2-diyl, propan-1,3-diyl, propan-1,2-diyl, butan-1,4-diyl, pentan-1,5-diyl, hexan-1,6-diyl, 2-methylbutan-1,4-diyl, 3-methylpentan-1,5-diyl and the like.

The term "alkenyl", alone or in combination, defines straight and branched chained hydrocarbon radicals containing from 2 to about 18 carbon atoms, preferably from 2 to 8 carbon atoms, more preferably 2 to 6 carbon atoms and even more preferably 2 to 4 carbon atoms, containing at least one double bond such as, for example, ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like.

The term "alkynyl", alone or in combination, defines straight and branched chained hydrocarbon radicals having from 2 to 10 carbon atoms containing at least one triple bond, more preferably from 2 to about 6 carbon atoms and even more preferably 2 to 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, propargyl, butynyl, pentynyl, hexynyl and the like.

The term "cycloalkyl" alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or polycyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms, more preferably from about 3 to about 7 carbon atoms. Examples of monocyclic cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclodecyl and the like. Examples of polycyclic cycloalkyl radicals include decahydronaphthyl, bicyclo [5.4.0] undecyl, adamantyl, and the like.

The term "aryl" alone or in combination, is meant to include phenyl and naphtyl which both may be optionally substituted with one or more substituents independently selected from alkyl, alkenyl, alkynyl, hydroxy, halogen, nitro, cyano, amino, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl, R^9-O-, R^9-S-, R^9-S(=O)$_2$-, R^9C(=O)-, R^9-C(=S)-, R^9-C(=NH)-, R^9-C(=NCN)-, R^9-NH-, $(R^9)_2$-N-, HO-C(=O)-, NH_2-C(=O)-, NH_2-S(=O)$_2$-, NH_2-C(=S)-, NH_2-C(=NH)-, NH_2-C(=NCN)-, R^9-NR^4-C(=O)-, R^9-NR^4-S(=O)$_2$-, R^9-O-C(=O)-, R^9-C(=O)-NR^4-, R^9-S(=O)$_2$-NR^4-, R^9-C(=O)-O- or phenyl optionally substituted with one or more substituents selected from alkyl, alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloalkyl, carboxyl, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, optionally mono- or disubstituted aminocarbonyl, alkylthio and alkylsulfonyl; whereby the optional

substituents on any amino function are independently selected from alkyl, alkyloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkyloxy, heterocycloalkyloxy-alkyl, phenyl, phenyloxy, phenyloxyalkyl, phenylalkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the latter amino groups may optionally be mono- or where possible di-substituted with alkyl. Examples of aryl includes phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 3-methyl-4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3-nitrophenyl, 3-aminophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methyl-3-acetamidophenyl, 2-methyl-3-aminophenyl, 3-methyl-4-aminophenyl, 2-amino-3-methylphenyl, 2,4-dimethyl-3-aminophenyl, 4-hydroxyphenyl, 3-methyl-4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, 3-amino-1-naphthyl, 2-methyl-3-amino-1-naphthyl, 6-amino-2-naphthyl, 4,6-dimethoxy-2-naphthyl and the like.

Wherever used, unless specified otherwise, the variable R^9 represents alkyl, cycloalkyl, heteroaryl, heterocycloalkyl or phenyl optionally substituted with one or more substituents selected from alkyl, alkyloxy, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloalkyl, carboxyl, alkoxycarbonyl, cycloalkyl, heterocycloalkyl, optionally mono- or disubstituted aminocarbonyl, alkylthio and alkylsulfonyl; whereby the optional substituents on any amino function are independently selected from alkyl, alkyloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkyloxy, heterocycloalkyloxyalkyl, phenyl, phenyloxy, phenyloxyalkyl, phenylalkyl, alkyloxycarbonylamino, amino, and aminoalkyl whereby each of the latter amino groups may optionally be mono- or where possible di-substituted with alkyl.

The term "haloalkyl" alone or in combination, means an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen, preferably, chloro or fluoro atoms, more preferably fluoro atoms. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like.

The term "heteroaryl" alone or in combination, means an aromatic monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 14 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulphur and which is optionally substituted on one or more carbon atoms by C_{1-6}alkyl, C_{1-6}alkyloxy, aminoC_{1-6}alkyl, halogen, hydroxy, optionally mono- or disubstituted amino, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl, Het^1 and an aromatic monocyclic, bicyclic or tricyclic heterocycle having 3 to 12 ring members; whereby the

optional substituents on any amino function are independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, Het^1-, Het^1C_{1-6}alkyl, Het^1C_{1-6}alkyl, Het^1oxy, Het^1oxyC_{1-4}akyl, aryl, aryloxy, aryloxyC_{1-4}alkyl, arylC_{1-6}alkyl, C_{1-6}alkyloxycarbonylamino, amino, aminoC_{1-6}alkyl and aminoC_{1-6}alkyl whereby each of the amino groups may optionally be mono- or where possible di-substituted with C_{1-4}alkyl.

The term "heterocycloalkyl" alone or in combination, means a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having preferably 3 to 14 ring members, more preferably 5 to 10 ring members and more preferably 5 to 6 ring members, which contains one or more heteroatom ring members selected from nitrogen, oxygen or sulphur and which is optionally substituted on one or more carbon atoms by C_{1-6}alkyl, C_{1-6}alkyloxy, aminoC_{1-6}alkyl, halogen, hydroxy, oxo, optionally mono- or disubstituted amino, optionally mono- or disubstituted aminoalkyl, nitro, cyano, haloC_{1-6}alkyl, carboxyl, C_{1-6}alkoxycarbonyl, C_{3-7}cycloalkyl, optionally mono- or disubstituted aminocarbonyl, methylthio, methylsulfonyl, aryl and a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle having 3 to 14 ring members; whereby the optional substituents on any amino function are independently selected from C_{1-6}alkyl, C_{1-6}alkyloxy, Het^2-, Het^2C_{1-6}alkyl, Het^2C_{1-6}alkyl, Het^2oxy-, Het^2oxyC_{1-4}akyl-, aryl-, aryloxy-, aryloxyC_{1-4}alkyl-, arylC_{1-6}alkyl-, C_{1-6}alkyloxy-carbonylamino-, amino-, aminoC_{1-6}alkyl and aminoC_{1-6}alkyl- whereby each of the amino groups may optionally be mono- or where possible di-substituted with C_{1-4}alkyl.

The term "alkyloxy" alone or in combination, defines straight and branched chained saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-6}alkyloxy and pentyloxy, hexyloxy, 2-methylbutyloxy, 3-methyl-pentyloxy and the like.

The term "cycloalkyloxy" alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or polycyclic alkyloxy radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms, more preferably from about 3 to about 7 carbon atoms. Examples of monocyclic cycloalkyloxy radicals include cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, cyclodecyloxy and the like.

As used herein, the term C(=O) forms a carbonyl moiety, the term C(=S) forms a thiocarbonyl moiety, the term S(=O) forms a sulfoxyl moiety, the term $S(=O)_2$ forms a sulfonyl moiety, the term C(=NH) forms an imino moiety and the term C(=NCN) forms a cyanoimino moiety.

Experimental part

The following compounds exemplify the present invention and are tested in an HIV entry assay. The results column represent the percent inhibition obtained of 100 micromolar.

Table 1.

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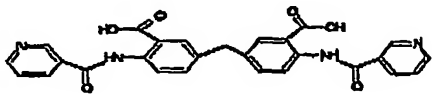	
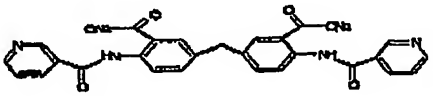	
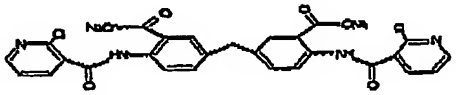	
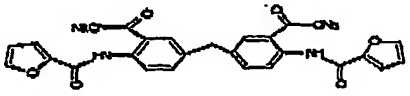	
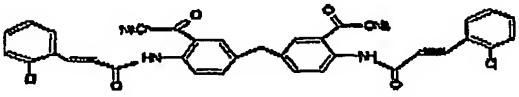	
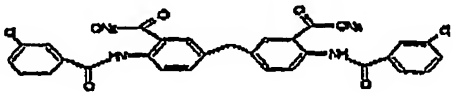	

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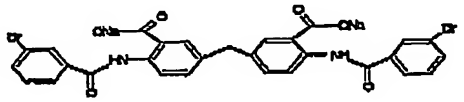	
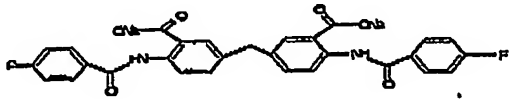	
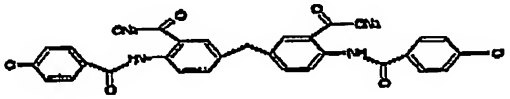	
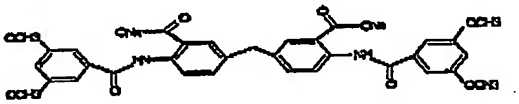	
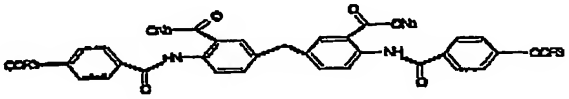	
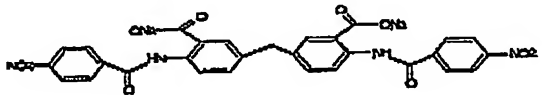	
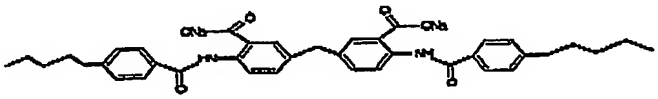	
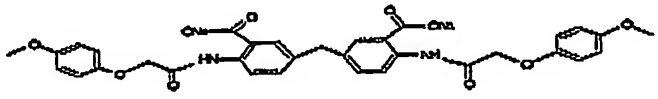	

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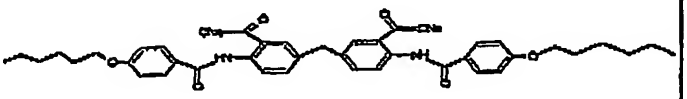
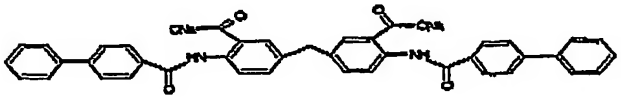
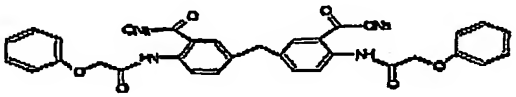
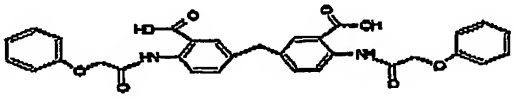
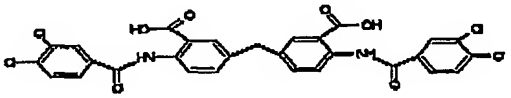
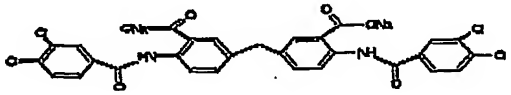
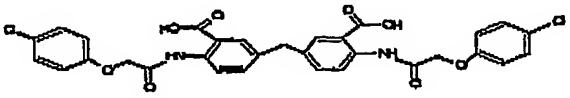
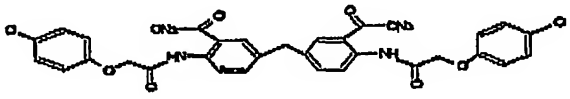
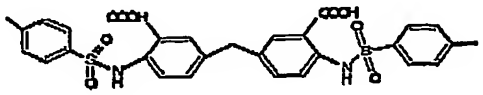
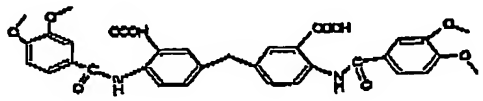
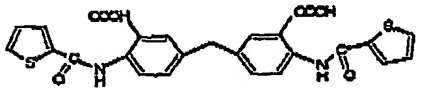
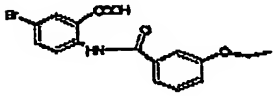
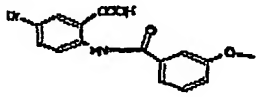
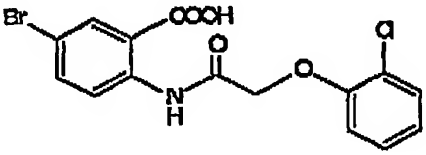
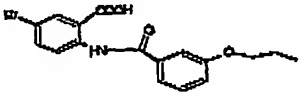
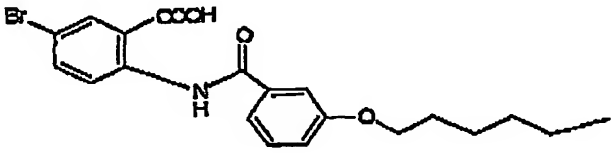
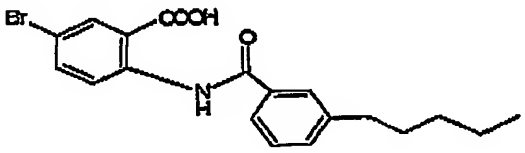
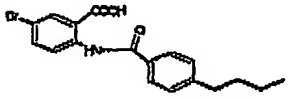
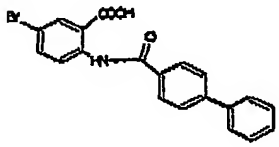
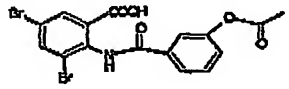
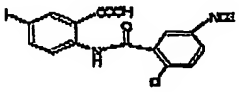
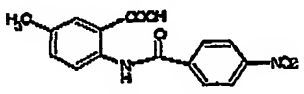
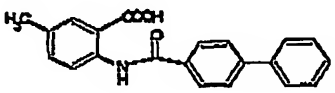
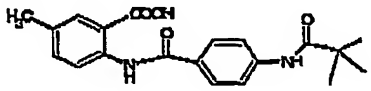
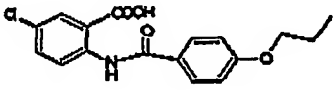
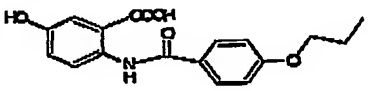
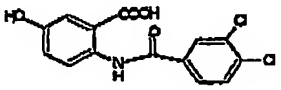
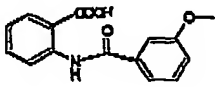
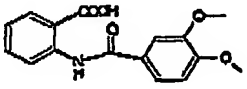
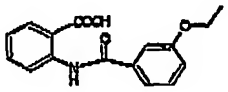
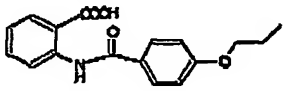
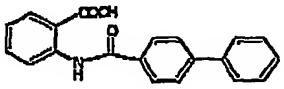
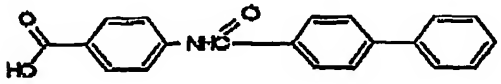
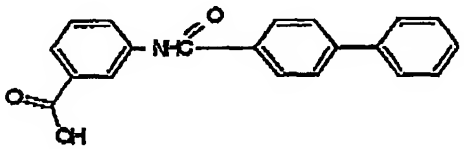
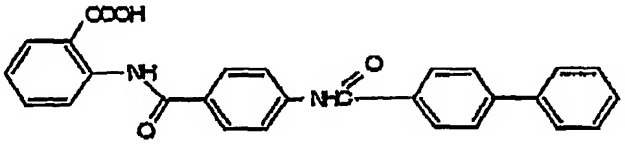
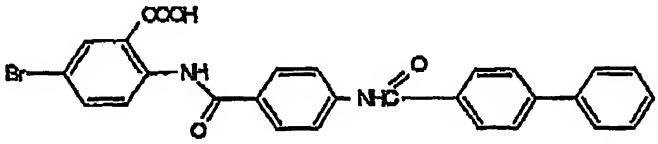
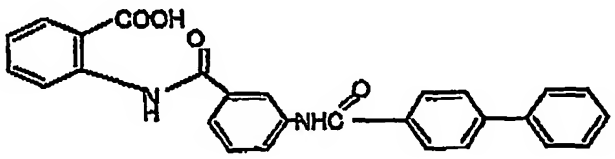
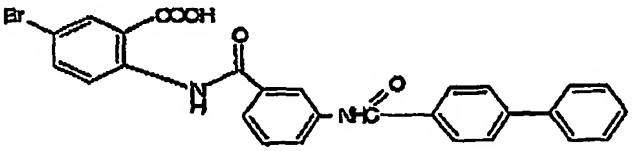
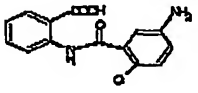
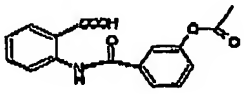
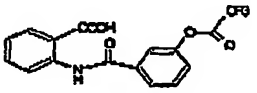
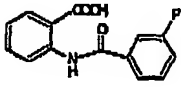
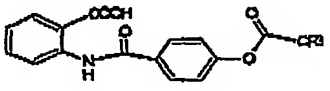
	
	
	
	
	
	
	
	

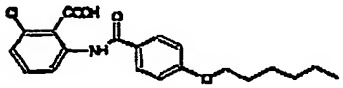
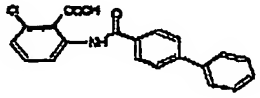
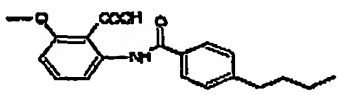
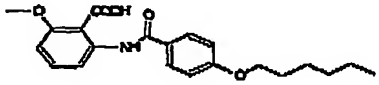
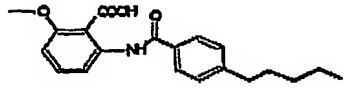
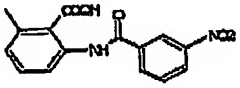
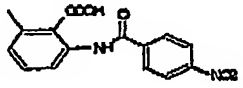
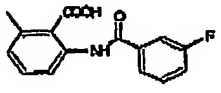
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100µm
	
	
	
	
	39.67
	32
	73.3

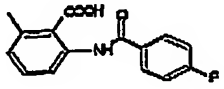
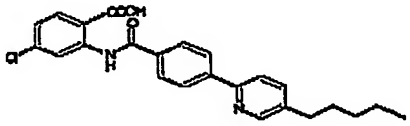
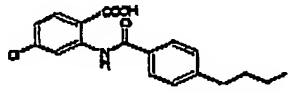
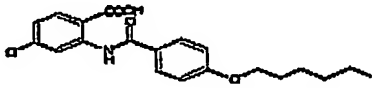
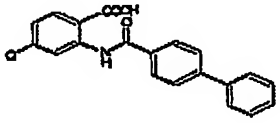
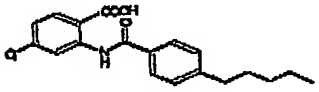
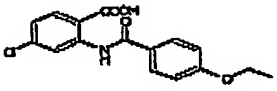
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100µm
	100
	
	
	
	3.5
	
	28

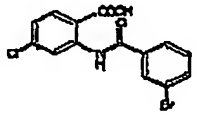
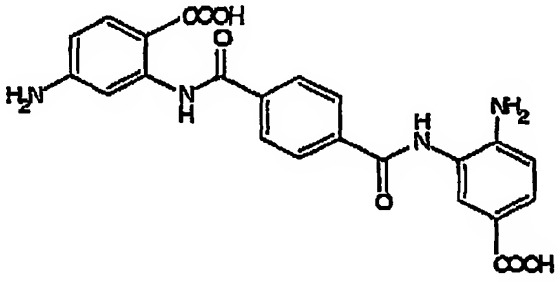
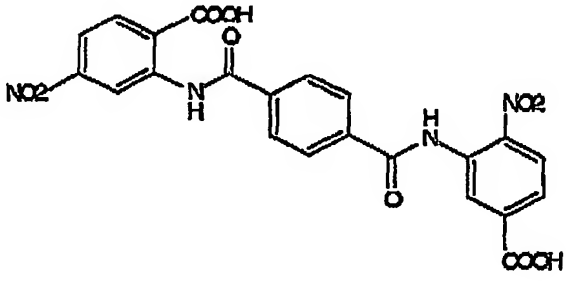
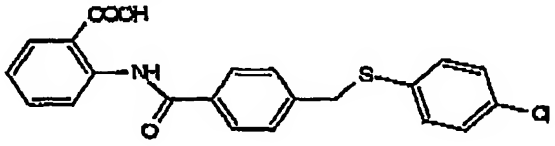
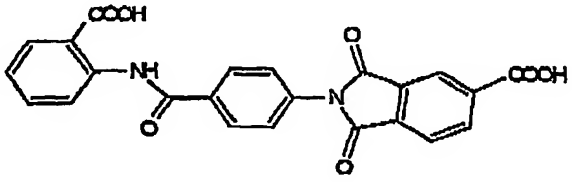
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100μm
	49
	10
	23
	6.7
	67
	100
	18
	

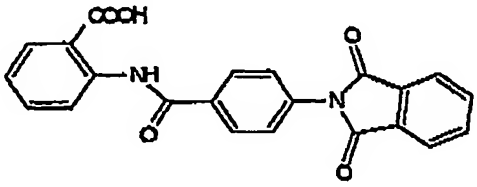
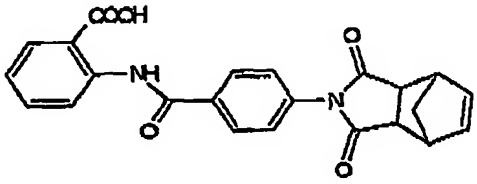
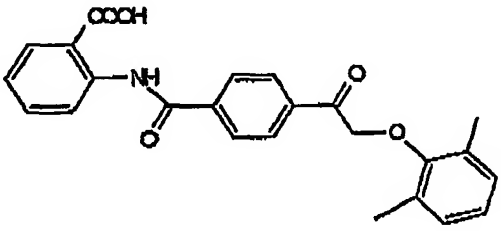
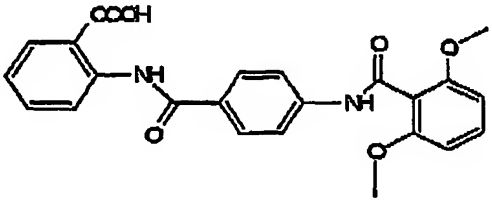
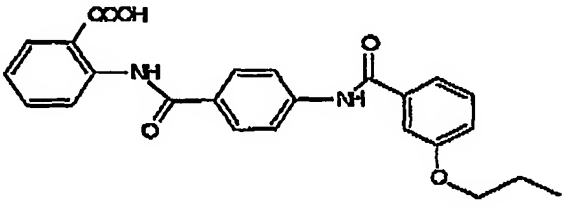
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100μm
	17
	90
	
	
	
	

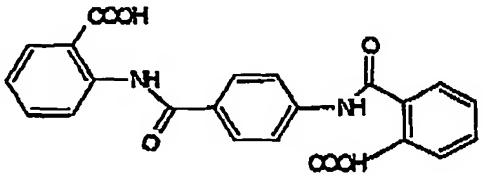
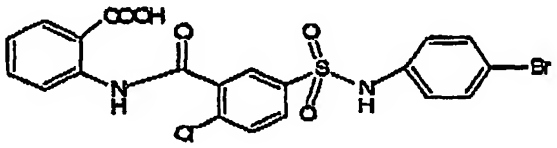
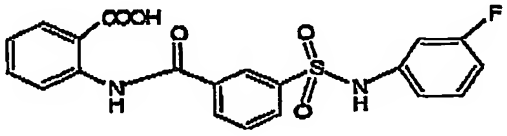
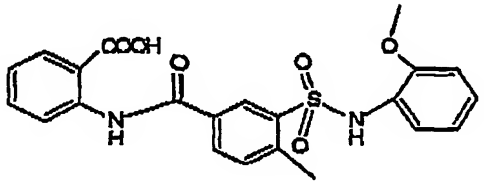
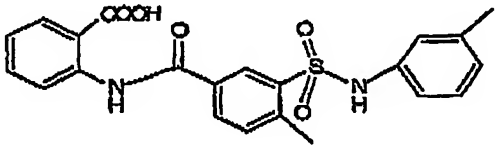
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100µm
	
	
	
	8.5
	31
	
	11
	100

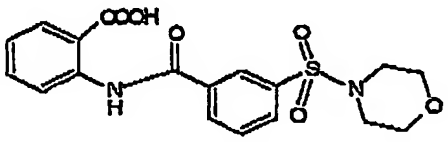
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100μm
	
	
	
	10
	10
	
	28
	5

COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100µm
	
	
	
	
	
	
	32

COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100μm
	
	175
	124
	138
	18

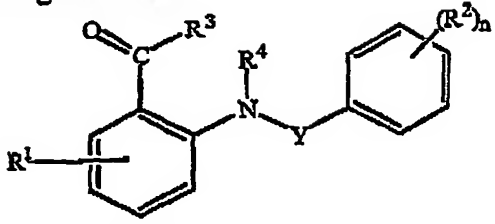
COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100µm
	23
	21
	65
	87
	

COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100µm
	75
	92
	34
	52
	76

COMPOUNDS OF THE PRESENT INVENTION	Inh.% 100μm
	

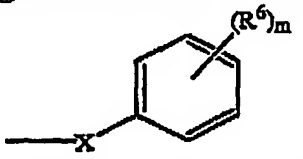
Claims

1. A compound having the formula



(I)

a N-oxide form, a stereochemical isomer, salt or prodrug thereof, wherein
R^1 represents halogen, hydrogen or a radical of formula (II)



(II)

R^2 represents alkyl, alkenyl, alkynyl, hydroxy, halogen, nitro, cyano, amino, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, R^8-O-, R^8-S-, R^8-S(=O)2-, R^8-C(=O)-, R^8-C(=S)-, R^8-C(=NH)-, R^8-C(=NCN)-, R^8-NH-, $(R^8)_2$-N-, HO-C(=O)-, NH_2-C(=O)-, NH_2-S(=O)$_2$-, NH_2-C(=S)-, NH_2-C(=NH)-, NH_2-C(=NCN)-, R^8-NR^4-C(=O)-, R^8-NR^4-S(=O)$_2$-, R^8-O-C(=O)-, R^8-C(=O)-NR^4-, R^8-S(=O)$_2$-NR^4- or R^8-C(=O)-O-;
R^5 represents alkyl, alkenyl, alkynyl, hydroxy, halogen, nitro, cyano, amino, haloalkyl, cycloalkyl, aryl, heteroaryl, heterocycloalkyl, R^8-O-, R^8-S-, R^8-S(=O)2-, R^8-C(=O)-, R^8-C(=S)-, R^8-C(=NH)-, R^8-C(=NCN)-, R^8-NH-, $(R^8)_2$-N-, HO-C(=O)-, NH_2-C(=O)-, NH_2-S(=O)$_2$-, NH_2-C(=S)-, NH_2-C(=NH)-, NH_2-C(=NCN)-, R^8-NR^4-C(=O)-, R^8-NR^4-S(=O)$_2$-, R^8-O-C(=O)-, R^8-C(=O)-NR^4-, R^8-S(=O)$_2$-NR^4- or R^8-C(=O)-O-;

R^4 represents hydrogen, alkyl or cycloalkyl;

R^3 represents hydroxy, amino, alkyloxy, cycloalkyloxy or mono- or disubstituted amino whereby the substituents can be selected from alkyl and cycloalkyl;
R^7 represents hydroxy, amino, alkyloxy, cycloalkyloxy or mono- or disubstituted amino whereby the substituents can be selected from alkyl and cycloalkyl;

R^8 represents alkyl, cycloalkyl, aryl, heteroaryl or heterocycloalkyl;

R^6 is hydrogen, amino, R^7-C(=O)-, R^8-S(=O)$_2$-NH-, R^8-C(=O)-NH-, R^8-C(=S)-NH-, R^8-C(=NH)-NH-, R^8-C(=NCN)-NH-, R^8-O-C(=O)-NH-, R^8—O-alkanediyl-C(=O)-NH-, R^8-alkanediyl-S(=O)$_2$-NH-, aryl-alkanediyl-C(=O)-NH-, heteroaryl-alkanediyl-C(=O)-NH-, cycloalkyl-alkanediyl-C(=O)-NH-, heterocycloalkyl-alkanediyl-C(=O)-

NH-, or alkyl substituted with amino, R^7-C(=O)-, R^8-S(=O)$_2$-NH-, R^8-C(=O)-NH-, R^8-C(=S)-NH-, R^8-C(=NH)-NH-, R^8-C(=NCN)-NH-, R^8-O-C(=O)-NH-, R^8—O-alkanediyl-C(=O)-NH-, R^8-alkanediyl-S(=O)$_2$-NH-, aryl-C_{1-6}alkanediyl-C(=O)-NH-, heteroaryl-alkanediyl-C(=O)-NH-, cycloalkyl-alkanediyl-C(=O)-NH- or heterocycloalkyl-alkanediyl-C(=O)-NH-;

Y represents alkanediyl, -C(=O)-, -C(=S)-, -C(=NH)-, -C(=NCN)-, -S(=O)-, -S(=O)$_2$-, -C(=O)-CH_2-O-, -C(=O)-O-, -C(=O)-$(CH_2)_p$-;

X is a direct bond, –O- , -S-, -S(=O)$_2$-, -O-S(=O)$_2$, -S(=O)$_2$-O-, -NH-S(=O)$_2$, -S(=O)$_2$-NH-, -C(=O)-, -C(=S)-, -C(=NH)-, -C(=NCN)-, -O-C(=O), -C(=O)-O-, -NH-C(=O), -C(=O)-NH- or alkanediyl;

n is zero, 1 or 2;

p is an integer from 1 to 4.

2. A compound as claimed in claim 1 and wherein the compound is a compound of table 1.

3. A compound as claimed in claim 1 or 2 for use as a medicine.

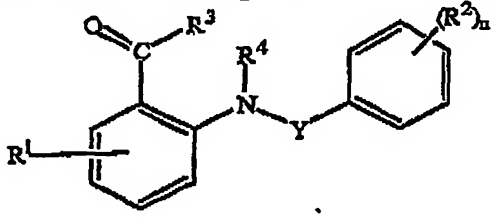
4. The use of a compound as claimed in claim 1 or 2 for the manufacture of a medicament capable of inhibiting the entry process of the HIV virus into a mammalian host cell.

5. A pharmaceutical composition containing a therapeutically effective amount of an active ingredient as claimed in claim 1 or 2 and one or more pharmaceutically acceptable excipients.

ABSTRACT

SMALL MOLECULE ENTRY INHIBITORS

The present invention concerns a compound having the formula



(I)

a N-oxide form, a stereochemical isomer, salt or prodrug thereof. It further relates to pharmaceutical compositions containing them, as well as their use as medicines. The present invention also relates to their chemical preparation